Office Action Summary	Application No.	Applicant(s)	
	10/526,325	CAPALDI ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-24,26,30-34,36,38,41-46 and 49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-24, 26, 30-34, 36, 38, 41-46, and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Please note that the examiner of record for your application has changed. To aid in paper matching, please address all future correspondence to Michael Szperka, Art Unit 1644, Technology Center 1600.

Applicant's response and amendments received October 9, 2008 is acknowledged.

Claims 1-18, 25, 27-29, 35, 37, 39, 40, 47, and 48 have been canceled.
Claim 19 has been amended.
Claims 19-24, 26, 30-34, 36, 38, 41-46, and 49 are pending in the instant application.

Applicant's claim amendments received October 9, 2008 have overcome all prior grounds of rejection. However, upon reconsideration, the following new grounds of rejection are set forth. As such, prosecution has been reopened and the finality of the office action mailed July 9, 2008 has been withdrawn.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 41 and 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Old et al. (Ann Neurol, 1989, 26:746-51, abstract only).

Old et al. disclose that children with lactic acidemia comprise reduced amounts of the PDH complex as compared to normal controls as measured by Western blotting.

(see entire abstract). Note that SDS-PAGE is a necessary step in performing Western blotting procedures.

Therefore, the prior art anticipates the claimed invention.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 41 and 44-46 rejected under 35 U.S.C. 103(a) as being unpatentable over Old et al. (Ann Neurol, 1989, 26:746-51, abstract only) in view of Janeway et al. (Immunobiology, 3rd edition, Garland Publishing, 1997, pages 2:20-2:23).

Old et al disclose methods of detecting reduced amounts of PDH complexes in children with lactic academia by western blot as discussed above and differ from the instant claimed invention in that they do not disclose detecting differences in the amount of PDH complex by other immunological methodologies.

Janeway et al. disclose that antibodies can be used in numerous ways in assay methods, and that the advantage of using an assay comprising antibodies is that the antibody provides the ability to very efficiently and specifically isolate the antigen of interest in complex mixtures of antigens (see entire selection). Such assay formats include immunofluorescence, indirect immunofluorescence, immunoprecipitation, ELISAs, and Western blotting (ibid).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the instant invention was made to modify the assay of Old et al. to detect decreases in the amount of PDH complex by other routine, art recognized immunoassay formats, such as those disclosed by Janeway et al. Note that an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982) and MPEP 2144.06.

6. Claims 19, 20, 22-24, 26, 30-34, 38 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Surh et al. (J. Immunol. 1990, 144:2647-2652, of record) in view of Kolobova et al. (Biochem. J., 2001, 358:69-77) in view of Wu et al. (Biochem J., 1998, 329:197-201) in view of Fuller et al (Biochem J., 1984, 219:635-646) and in view of Janeway et al. (Immunobiology, 3rd edition, Garland Publishing, 1997, pages 2:20-2:23).

Surh et al. disclose assays for determining the activity of the pyruvate dehydrogenase (PDH) complex, such assays involving the binding of the PDH complex to a solid support using antibodies specific for PDH and measuring complex activity via monitoring NADH production (see entire document, particularly the right column of page 2648). The antibodies of Surh et al. are specific for E2 (see particularly the abstract). These teachings differ from the instant claimed invention in that they do not disclose measuring the phosphorylation state of the PDH complex.

Kolobova et al. disclose that the activity of the PDH complex is regulated by phosphorylation of the enzyme complex (see entire document, particularly the abstract). They disclose assays wherein phosphorylation of the complex was assayed by incorporation of radioactive phosphate groups, along with measurements of ATP-dependent inactivation of the PDH complex by spectrophotometically following the production of NADH (see particularly the right column of page 70). As part of such assays, Kolobova et al. also made mutants of E1 and used said assays to determine how activity of the PDH complex was changed in the presence and absence of PDK

enzymes which inactivate the PDH complex and TPP which activates the PDH complex. Note that SDS-PAGE was used in the assays to detect phosphorylation, and that a shift in mobility was observed when comparing wild type to mutant complexes (see particularly figure 2).

Wu et al. disclose that the activity of the PDH complex is markedly reduced in diabetes, that phosphorylation reduces the activity of said complex, and that the amount and activity of kinases, particularly PDK4, are increased in the diabetic state, thus leading to the observed loss of activity for PDH complexes in the diabetic state (see entire document, particularly the abstract, introduction and discussion). Such an impairment of PDH complex activity exacerbates the impaired glucose oxidation and insulin resistance characteristic of non-insulin-dependent diabetes mellitus (ibid).

Fuller et al. disclose assays for measuring the activity of the PDH complex, and that the complex can be inactivated by ATP and activated by pyruvate and dicloroacetic acid (see entire document, particularly the abstract). They also disclose that while the total amount of the PDH complex was unchanged between diabetic samples and normal controls, the amount of active PDH complexes were reduced in diabetic samples as compared to normal controls (see particularly page 1984).

Janeway et al. disclose that antibodies can be used in numerous ways in assay methods, and that the advantage of using an assay comprising antibodies is that the antibody provides the ability to very efficiently and specifically isolate the antigen of interest in complex mixtures of antigens (see entire selection). Such assay formats include immunofluorescence, indirect immunofluorescence, immunoprecipitation, ELISAs, and Western blotting (ibid).

Therefore, the claimed assay method would have been obvious to a person of ordinary skill in the art at the time the instant invention was made. Motivation to do so comes from the teachings of Wu et al. and Fuller et al. that the activity of the PDH complex is correlated with the diabetic state. As such, it would be obvious to a person of ordinary skill in the art that if a variable, such as PDH complex activity, is known to be correlated with a particular disease, for example, diabetes, that such a relationship forms the basis for a diagnostic assay. Specifically, if a person of ordinary

skill in the art were to measure PDH activity in a sample and finds that said activity is decreased as compared to a control, the person of ordinary skill in the art would reasonably conclude that the sample may have come from a diabetic patient since it was known that diabetic patients comprise impaired PDH activity. The prior art discloses numerous ways to measure such activity, and a person of ordinary skill in the art would be motivated to use an assay that detects both NADH and phosphorylation, such as those of Kolobova et al., since Wu et al. discloses that the amount and activity of an enzyme which phosphorylates and thus inactivates the PDH complex is upregulated in the diabetic state. Incorporation of antibodies specific for the complex would aid in isolating the PDH complex from a patient sample as disclosed by Janeway et al. and an ordinary artisan would have a reasonable expectation of success in using such antibodies based upon the assays utilizing antibodies disclosed by Surh et al. Therefore, since it was known that decreased PDH activity was correlated with diabetes, it would have been obvious to a person of ordinary skill in that art that any assay format disclosed in the prior art to determine PDH complex activity could be used and combined to determine PDH activity for the purpose of detecting diabetes. Note that "It is prima facie obvious to combine two compositions (or methods) each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition (method) to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). See also MPEP 2144.06. Further, note also that an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982) and MPEP 2144.06.

7. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Surh et al. (J. Immunol. 1990, 144:2647-2652, of record) in view of Kolobova et al. (Biochem. J., 2001, 358:69-77) and in view of Wu et al. (Biochem J., 1998, 329:197-201) in view of Fuller et al (Biochem J., 1984, 219:635-646) in view of Janeway et al. (Immunobiology,

3rd edition, Garland Publishing, 1997, pages 2:20-2:23) as applied to claims 19, 20, 22-24, 26, 30-34, 38 and 49 above, and further in view of Barnes et al. (Clin Chim Acta 1980, 107:149-54, abstract only).

The inventions rendered obvious by the disclosures of Surh et al., Kolobova et al., Wu et al., Fuller et al., and Janeway et al. have been discussed above and differ from the instant claimed invention in that they do not disclose the use of resazurin as an electron acceptor when making dehydrogenase determinations.

Barnes et al. disclose that when NADH is oxidized using resazurin as an electron acceptor, the fluorescently measurable product resorufin was produced and that such an assay is to be used for determining dehydrogenase concentrations (see entire abstract).

Therefore, it would have been obvious to a person of ordinary skill in the art to modify the assays rendered obvious by the disclosures of Surh et al., Kolobova et al., Wu et al., Fuller et al., and Janeway et al. to include resazurin since such assays already comprise measuring NADH photometrically and the use of resazurin generates a fluorescent molecule which is readily detected photometrically. Note that an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982) and MPEP 2144.06.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 42 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant has claimed a method wherein diagnosis of a disease is made by determining that a patient sample comprises a reduced amount of the PDH complex as compared to a normal individual. One of the specifically recited diseases is diabetes. Fuller et al. disclose that while the activity of the PDH complex is reduced in diabetic rats, the total concentration of the PDH complex is unchanged between diabetic and normal samples (see particularly the right column of page 1984). The instant specification does not appear to disclose data that the total concentration of the PDH complex is decreased in diabetes. Thus, while it is clear that the activity of the PDH complex is reduced in diabetes, it does not appear that the absolute mass of PDH complexes in diabetes is reduced.

Therefore, based upon the breadth of the claimed invention, the guidance and examples of the specification, and the teachings of the art, a skilled artisan would be unable to practice the invention as currently recited.

Claim Objections

10. Claim 30 is objected to because it comprises a period before a comma in the middle of the third line. Appropriate correction is required.

11. No claims are allowable.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is (571)272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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